UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,523	12/17/2001	Ann M. Lees	10797-004004	5012

26161 7590 07/23/2004

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
MITRA, RITA	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	10/023,523	LEES ET AL.	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-95* is/are pending in the application.

4a) Of the above claim(s) *38-42,58-62,89,90,92 and 94* is/are withdrawn from consideration.

5)☒ Claim(s) *46,50,51,64 and 68* is/are allowed.

6)☒ Claim(s) *43-45,47-49,52-57,63,65-67,69-88,91,93 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Restriction Election

Applicants' response to the Restriction Requirement dated April 7, 2004 filed on May 6, 2004 is acknowledged. Applicants have elected the invention of Group III, claims 47-51, 55-57, 67-70, 72, 76-78 with traverse. Applicants' request for joining the claims of Groups II, VII and VIII be examined together with the claims of Group III. The grounds for traversal is that the pending claims are directed to nucleic acid sequence encoding a novel human LDL-binding polypeptide termed LBP-3, wherein the LBP-3 is a full-length protein having amino acid sequence of SEQ ID NO: 44 (Group III) and SEQ ID NO: 8 (amino acids 17-546 of human LBP-3) (Group II) is a fragment of SEQ ID NO: 44, wherein the SEQ ID NO: 46 (Group VIII) is a specific nucleotide sequence encoding SEQ ID NO: 44 and SEQ ID NO: 17 (Group VII) is a specific nucleotide sequence encoding SEQ ID NO: 8. Applicants further indicates that because SEQ ID NO: 46 and 17 are merely nucleotide sequences that encode these polypeptides, the issues raised during the course of prosecution of these human LBP-3 nucleic acid sequences are expected to be similar and simultaneous examination is therefore not expected to be unduly burdensome. Applicants request has been considered and in light of the above comments claims of Groups II, VII and VIII have been rejoined with the claims of Group III. Therefore, claims 43-57, 63-88, 91, 93 and 95 are pending and are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-45, 47-49, 52-54, 55-57, 63, 65-67, 69-88, 91, 93, 95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 43-45, 47-49, 52-54, 55-57, 63, 65, 66, 67, 69, 70, 71, 72, 73-75, 76-78, 79-88, 91, 93, 95 encompass the subject matter that is not defined in the specification. The claims are directed to an isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence that binds to LDL comprising an amino acid sequence of SEQ ID NO: 8 or of SEQ ID NO: 44. The specification does not describe what might be considered a "LDL binding" variants of the claims 43-45, 47-49, 52-54, 55-57 and fragments of the claims 63, 65, 66, 67, 69, 70 and mutants of claims 71, 72, 73-78. Identification of the nucleotide sequence (SEQ ID NO: 47) encoding the full length LDL binding polypeptide (Fig. 8A, SEQ ID NO: 47 and 44; Fig. 8B, SEQ ID NO: 8 and Fig. 17, SEQ ID NO: 17) is described (see specification page 8-12) and exemplified in the specification (Examples 5, 8 and 9 LBP-1, LBP-2 or LBP-3), however specification fails to provide any description or demonstration of a variant of polynucleotide sequence of SEQ ID NO: 46 and SEQ ID NO: 17 that retains the activity of the full length polynucleotide sequence of SEQ ID NO: 46 and SEQ ID NO: 17.

The claims 63, 65, 66, 67, 69, 70 are directed to an isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide comprising at least 10 or 20 or 30 amino acid residues of amino acid sequence disclosed in SEQ ID NO: 8 (claim 63, 65, 66) and SEQ ID NO: 44 (claim 67, 69, 70) respectively. It is clear from the specification that Applicants were in possession of SEQ ID NO: 46 encoding the amino acid sequence of SEQ ID NO: 44 and SEQ ID NO: 8 and SEQ ID NO: 17 at the time the invention was made. However, the specification, have given no concise definition of these variants. The specification indicates (see page 17-22), that analogs can be made by in vitro DNA sequence modifications of the sequences of SEQ ID NO: 46 or 17. For example, in vitro mutagenesis can be used to convert any of these DNA sequences which encodes an analog in which one or more amino acid residues has undergone a conservative replacement (page 19-20). The variants share structural similarity with LDL binding proteins and retain the biological activity of the full-length wild type protein, however the description is generic. The claims are directed to an isolated nucleic acids encoding a polypeptide, wherein the amino acid sequence is set forth in SEQ ID NO: 8 and SEQ ID NO: 44,

and variants thereof. However, the specification provides only a generic description of how a variety of fragments/variants can be generated (page 17-22), no specific information is provided on the generation of the fragments or variants that demonstrate the biological activity of the peptide sequence of SEQ ID NO: 8 or 44. Therefore, there is lack of written descriptions as to what are those variants of SEQ ID NO: 8 and SEQ ID NO: 44 that binds to low density lipoproteins.

Claims 79-83 are directed to an isolated nucleic acid comprising a nucleic acid sequence that specifically hybridizes to the sequence of SEQ ID NO: 17, wherein the nucleotide sequence encodes a polypeptide that binds to LDL, and at least 80% or 95% identical to the SEQ ID NO: 17. Claims 84-88 are directed to an isolated nucleic acid comprising a nucleic acid sequence that specifically hybridizes to the sequence of SEQ ID NO: 46, wherein the nucleotide sequence encodes a polypeptide that binds to LDL, and at least 80% or 95% identical to the SEQ ID NO: 46. The specification indicates at page 2 that isolated polynucleotide comprising a polynucleotide encoding the polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 44 or a polynucleotide capable of hybridizing to and which is at least 95% identical to the polynucleotide sequence that encodes an amino acid sequence of SEQ ID NO: 44 and the encoded polypeptide is capable of binding to LDL. However, the specification fails to describe a specific fragment of a polynucleotide that hybridizes to the sequence of SEQ ID NO: 46 or 17 and at least 80% or 95% identical to SEQ ID NO: 46 or 17. Also the condition of hybridization is not provided in the specification. Therefore, there is a lack of written description as to what are those fragments of polynucleotides that hybridize to and at least 80% or 95% identical to the sequence of SEQ ID NO: 46 or 17.

Claims 43-45, 47-49, 52-57, 63, 65, 66, 67, 69, 70, 71, 72, 73-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 52-54 are directed to an isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence that binds to LDL and is at least about 80%, 90%, or 95% identical to a portion of the amino acid sequence of SEQ ID NO: 8,

respectively, which binds to LDL. Claims 55-57 are directed to an isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence that binds to LDL and is at least 80%, 90%, or 95% identical to a portion of the amino acid sequence of SEQ ID NO: 44, respectively, which binds to LDL. Claims 63, 65 and 66 are directed to an isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence identical to a fragment of at least 10 or 20 or 30 amino acid residues of SEQ ID NO: 8, wherein the polypeptide binds to LDL. Claims 67, 69, 70 are directed to an isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence identical to a fragment of at least 10 or 20 or 30 amino acid residues of SEQ ID NO: 44, respectively, wherein the polypeptide binds to LDL.

The specification while defining the analogs indicates at page 17, last paragraph to page 18, first paragraph that analogs of the invention exhibit at least 80%, preferably 90%, more preferably 95% or most preferably 98% homology with substantially the entire sequence of a naturally occurring LBP sequence, preferably with a segment of about 100 or 50, or 30, or 10, or 5, or 4, or 3 or 2 amino acid residues. However, the specification fails to describe any analog that has at least 80% identity to a portion of the sequence set forth in SEQ ID NO: 8 (claims 52-54) and SEQ ID NO: 44 (claims 55-57) which have the LDL binding activity. There is no guidance provided to allow the skilled artisan to predict the portion of the SEQ ID NO: 8 or SEQ ID NO: 44 that would have had at least 80% identity to the claimed peptide sequence fragment encoded by a nucleic acid sequence.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include: 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those skilled in the art, 7) the predictability or unpredictability of the art and 8) the breadth of the claims.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

In the instant case, the amount of experimentation is enormous since the number of changes from the specific sequence are large, one of skill in the art would have to make and test each one to determine if it had the LDL binding activity of the parent protein.

Also the specification fails to describe or provide guidance about the nucleic acid sequence encoding the amino acid sequence having identity to a fragment of at least ten or twenty or thirty amino acid residues of SEQ NO: 8 (claims 63, 65, 66) or SEQ ID NO: 44 (claims 67, 69, 70). A skilled artisan would not have recognized what is the position of these 10, 20 or 30 amino acids in relation to the amino acid sequence set forth in SEQ ID NO: 8 and SEQ ID NO: 44. Although Examples 8 and 9 (pages 47-50) demonstrate the binding of LBP-2 (full length) and LDL by Affinity Co-Electrophoresis Assay (ACE), this is not demonstrative of any analogs that are claimed in claims 52-57 and claims 63, 65-67, 69, 70. There is no guidance provided to allow the skilled artisan to predict the nucleic acid sequence that encodes the portion of the SEQ ID NO: 8 and SEQ ID NO: 44 that would have had at least 80% identity to the claimed amino acid sequence fragment.

The specification does not provide a working Example that demonstrates the claimed variants.

The specification does not disclose what might be considered a "LDL binding" variants of the claims 43-45, 47-49, 52-54, 55-57 and fragments of the claims 63, 65, 66, 67, 69, 70 and mutants of claims 71, 72, 73-78 or provide any example of the same.

The nature of the variation makes it entirely unpredictable what might be considered a variant before the isolation of such a sequence has actually taken place.

Given the breadth of the claims in the invention, detailed teachings are required to be present in the disclosure in order to enable the skilled artisan to make and use the mutants/fragments/variants/analogs of broadly claimed group of nucleic acids encoding the LDL binding proteins. Such teachings are absent in the specification.

For these reasons it would require undue experimentation to make the claimed invention.

Claims 43-45, 52-54, 63, 65, 66, 71, 73-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid sequence encoding a polypeptide of an amino acid sequence set forth in SEQ ID NO: 8 that binds to low

density lipoprotein (LDL); does not reasonably provide enablement for all the nucleic acid sequence encoding LDL binding proteins, and fragments and mutants generated from any position located on the sequence of SEQ ID NO: 8. Claims 47-49, 55-57, 67, 69, 70, 72, 76-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid sequence encoding a polypeptide of an amino acid sequence set forth in SEQ ID NO: 44 that binds to low density lipoprotein (LDL); does not reasonably provide enablement for all the nucleic acid sequence encoding LDL binding proteins, and fragments and mutants generated from any position located on the sequence of SEQ ID NO: 44. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The specification, however, only discloses cursory conclusions (see page 17-22) to support the findings. See the discussion below.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include: 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those skilled in the art, 7) the predictability or unpredictability of the art and 8) the breadth of the claims.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The quantity of experimentation necessary:

In the instant case, the amount of experimentation is enormous since the number of changes from the specific sequence are large, one of skill in the art would have to make and test each one to determine if it had the LDL binding activity of the parent protein or the nucleic acid sequence encoding the protein. The specification has disclosed an LDL binding protein having an amino acid sequence of SEQ ID NO: 8 and SEQ ID NO: 44. The working examples are exclusively drawn to making one full-length LDL binding protein (LBP-1, LBP-2 or LBP-3) and characterizing cDNAs encoding the full-length protein (Examples 8, 9), however, the specification does not provide a working Example that demonstrates the claimed variants.

The amount of direction or guidance presented:

There is no guidance provided to allow the skilled artisan to predict the nucleic acid encoding the portion of the SEQ ID NO: 8 and SEQ ID NO: 44 that would have had at least 80% identity to the claimed amino acid sequence fragment. The specification indicates at page 18-19 and in Table 1 that preferred analogs include LBP or biologically active fragments thereof whose sequence differ from the wild type sequence by one or more conservative amino acid substitutions or by one or more non-conservative amino acid substitutions, deletions or insertions which do not abolish LBP biological activity. However, the specification fails to provide a variant, which has LBP biological activity. There is no disclosure about the biological activities of these claimed variants. Identification of the nucleotide sequence (SEQ ID NO: 47) encoding the full length LDL binding polypeptide (Fig. 8A, SEQ ID NO: 47 and 44; Fig. 8B, SEQ ID NO: 8 and Fig. 17, SEQ ID NO: 17) is described (see specification page 8-12) and exemplified in the specification (Examples 5, 8 and 9 LBP-1, LBP-2 or LBP-3), however the specification fails to provide any discussion of a variant of a nucleic acid sequence encoding a polypeptide of SEQ ID NO: 8 and SEQ ID NO: 44 that retains the activity of the full length polypeptide of SEQ ID NO: 8 and SEQ ID NO: 44. The amount of guidance presented is limited to the exact sequence. No discussion is present as to where the changes might be made to SEQ ID NO: 8 and SEQ ID NO: 44. An example of desirable guidance for a LDL binding protein would be disclosure of the binding domain, which is not present. There is no guidance as to how the functional fragments and variants of the claimed nucleic acid encoding the protein can be generated. The specification has provided no guidance to enable one of ordinary skill in the art to determine the positions in the protein, which are tolerant to change (e.g., by amino acid deletions, insertions or substitutions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active variants that may be constructed, because no specific guidance has been given in the specification.

The presence or absence of working examples:

The working examples are exclusively drawn to making one full-length LDL binding protein (LBP-1, LBP-2 or LBP-3) and characterizing cDNAs encoding the full-length protein (Examples 8, 9), however, the specification does not provide a working Example that demonstrates the claimed variants.

The nature of the invention:

The nature of the invention is defined by the claims, which include an isolated nucleic acid encoding a polypeptide that binds to LDL comprising an amino acid sequence of SEQ ID NO: 8 or of SEQ ID NO: 44. The specification does not disclose what might be considered a "LDL binding" variants of the claims 43-45, 47-49, 52-54, 55-57 and fragments of the claims 63, 65, 66, 67, 69, 70 and mutants of claims 71, 72, 73-78 or provide any example of the same.

The predictability or unpredictability of the art:

The nature of the variation makes it entirely unpredictable what might be considered a variant before the isolation of such a sequence has actually taken place. The effect of one or a few conservative substitutions might be somewhat predictable, if the active areas of the molecule were known, but more changes than that are less predictable.

The breadth of the claims:

The breadth of the claims is broad and encompasses an unspecified number of variants regarding the polypeptide of SEQ ID NO: 8 and SEQ ID NO: 44 as biological active variants encoded by nucleic acid sequence. Given the breadth of the claims in the invention, detailed teachings are required to be present in the disclosure in order to enable the skilled artisan to make and use the mutants/fragments/variants/analogs of broadly claimed group of LDL binding proteins. Such teachings are absent in the specification. The scope of the claims includes fragments, variants, analogs and mutants of polypeptide. However the specification does not provide the information on the structure and function of the claimed variants of the said polypeptide or the nucleic acid encoding those variants. The number of changes to result in a sequence with 80% identity to the starting sequence would, of course, be 20 changes per hundred

amino acids. The effects on function of this many changes is clearly unpredictable. Finally, these claims are very broad in the sense that a vast number of different nucleic acids encoding the proteins fall within the scope of the claims.

For these reasons, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 43-45, 47-49, 52-57, 64, 68, 71-78, 80, 85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 43, 47, 52, 55, 64, 68, 71, 72, 73, 76, 80, 85 are indefinite because of the use of the term "LDL." The full spelled out words should precede an acronym/abbreviation. Claims 44, 45, 48, 49, 53, 54, 56, 57, 74, 75, 77 and 78, are included in the rejection because they depend from rejected claims and do not correct the deficiency of the claims from which they depend.

Conclusion

Claims 43-45, 47-49, 52-57, 63, 65-67, 69-72, 73-78, 79-88, 91, 93, 95 are rejected. Claims 46, 50, 51, 64, 68, are allowable because a search of the prior art shows SEQ ID NO: 46, SEQ ID NO: 17 encoding SEQ ID NO: 44, SEQ ID NO: 8, respectively, to be novel and unobvious.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (571) 272-0954. The

Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Jon Weber, can be reached at (571) 272-0925. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette,1096 OG 30 (November 15, 1989). The Fax Center number is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0547.

Rita Mitra, Ph.D.
July 6, 2004

Jon P. Weber, Ph.D.
Primary Examiner